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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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David Wallach

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EXAMINER

STOICA, ELLY GERALD

ART UNIT

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1647

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PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No. 10/575,915	Applicant(s) WALLACH ET AL.	
	Examiner ELLY-GERALD STOICA	Art Unit 1647	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☐ Responsive to communication(s) filed on ____.
- 2a) ☒ This action is **FINAL**. 2b) ☐ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 2,3,5,7 and 63-71 is/are pending in the application.
 4a) Of the above claim(s) 5,7,64-68 and 70 is/are withdrawn from consideration.
- 5) ☐ Claim(s) ____ is/are allowed.
- 6) ☒ Claim(s) 2,3,63,69 and 71 is/are rejected.
- 7) ☐ Claim(s) ____ is/are objected to.
- 8) ☐ Claim(s) ____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on ____ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
 Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
 Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
 a) ☐ All b) ☐ Some * c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
 2. ☐ Certified copies of the priority documents have been received in Application No. ____.
 3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

- | | |
|--|---|
| 1) <input checked="" type="checkbox"/> Notice of References Cited (PTO-892) | 4) <input type="checkbox"/> Interview Summary (PTO-413)
Paper No(s)/Mail Date. ____. |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948) | 5) <input type="checkbox"/> Notice of Informal Patent Application |
| 3) <input type="checkbox"/> Information Disclosure Statement(s) (PTO/SB/08)
Paper No(s)/Mail Date ____. | 6) <input type="checkbox"/> Other: ____. |

DETAILED ACTION

Status of the claims

1. In the reply filed on 08/13/2008, Applicant amended claims 3,5, and 7, cancelled claims 8-11, 13-24, 26-31, 33-43, 45-47 and 49-62. Claims 63-71 were added. Claims 2, 3, 5, 7 and 63-71 are pending. Claims 5, 7, 64-68 and 70 are withdrawn for being drawn to non-elected species, the elected species being the antisense polynucleotide as the species of active agent and acute myelogenous leukemia as the disease, as indicated in the response filed 02/22/2008. Claims 2, 3, 63, 69 and 71 are currently examined.

Claim Objections

2. Claims 2 and 71 are objected to because of the following informalities: they contain non-elected subject matter.

Claim 69 is objected to since the claims should recite: "... the expression or an activity of an α 1 splice variant...".

Appropriate correction is required.

Claim Rejections - 35 USC § 112

3. The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

4. Claim 71 is rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim contains subject matter which was not

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described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

The factors considered when determining if the disclosure satisfies the enablement requirement and whether any necessary experimentation is "undue" include, but are not limited to:

1) nature of the invention, 2) state of the prior art, 3) relative skill of those in the art, 4) level of predictability in the art, 5) existence of working examples, 6) breadth of claims, 7) amount of direction or guidance by the inventor, and 8) quantity of experimentation needed to make or use the invention. In re Wands, 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988).

The claim is drawn to a method of inhibiting hematopoiesis in a subject comprising down regulating the expression or activity of caspase-8 by an antisense polynucleotide capable of specifically hybridizing with an mRNA transcript encoding caspase-8, wherein the polynucleotide is injected directly into bone marrow.

The invention is based on the practical concept of inhibition of the expression of a gene product and consequently of the activity of the gene product in living cells. The prior art offers examples of individual genes being inhibited at mRNA level by antisense polynucleotides. The field of inhibition of protein expression and/or activity by using antisense oligonucleotides is advanced. However, the delivery of the antisense is performed in experimental conditions in vitro. Moreover, the antisense polynucleotide is delivered through specialized vectors or liposomes; naked polynucleotides are not known and not predicted to survive in the environmental milieu of a living tissue and

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penetrate a cellular membrane. There is no account of caspase 8 antisense nucleotide delivered directly to bone marrow for inhibiting hematopoiesis. The specification does not offer any guidance in this respect and the only working examples are related to caspase 8 knock-out mice (in which the caspase 8 gene is not expressed at all). This model system does not prove that by blocking the gene expression with exogenous antisense nucleotide would necessarily work even in cell culture. Moreover, the prophetic concept of inhibiting the hematopoiesis by delivering caspase 8 antisense polynucleotides directly to the bone marrow of a patient is even more uncertain, since antisense nucleotides are not known to enter into cell without a vector or a carrier. The amount of experimentation needed to obtain inhibition of hematopoiesis by direct injection of antisense nucleotides into bone marrow is considered undue.

Claim Rejections - 35 USC § 102

5. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

6. Claim 2 remains and claims 3 and 69 are rejected under 35 U.S.C. 102(b) as being anticipated by Zhang et al. (U.S. Pub No. 20030083296, 05/01/2003) for reasons of record.

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Zhang et al. teach compositions comprising antisense compounds, particularly antisense oligonucleotides, targeted to nucleic acids encoding caspase 8 and methods of using these compounds for modulation of caspase 8 expression and for treatment of diseases associated with expression of caspase 8 (abstract). The antisense compounds specifically hybridize with one or more nucleic acids encoding caspase 8 (DNA encoding caspase 8, RNA (including pre-mRNA and mRNA), transcribed from such DNA, and also cDNA derived from such RNA). The specific hybridization of an oligomeric compound with its target nucleic acid interferes with the normal function of the nucleic acid. This modulation of function of a target nucleic acid by compounds which specifically hybridize to it is generally referred to as "antisense". The functions of DNA to be interfered with include replication and transcription. The functions of RNA to be interfered with include all vital functions such as, for example, translocation of the RNA to the site of protein translation, translation of protein from the RNA, splicing of the RNA to yield one or more mRNA species, and catalytic activity which may be engaged in or facilitated by the RNA. The overall effect of such interference with target nucleic acid function is modulation of the expression of caspase 8 ([0014]). One of the methods of treatment specifically names a hematopoietic disorder (claim 18).

On page 6-7 of the Remarks Applicant argues that the Zhang et al. reference is not enabled. The arguments were carefully considered but not found persuasive because first of all, in the examples 1-15 Zhang et al. have working examples of inhibiting caspase 8 by using antisense oligonucleotides. The oligonucleotides would perform the same activity, inhibiting the caspase activity in any cell that expresses it,

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irrespective of the desire of the person practicing the antisense inhibition. Zhang et al. claimed the use of the oligonucleotides for treating hematopoietic disorders, based on what was known in the art. Contrary to the Applicants arguments on pages 7-8, that contend that Zhang et al. does not teach inhibiting hematopoiesis, one of the components of the causes of hematopoietic disorders in hematopoiesis itself. Zhang et al. contains for instance reference to the U.S. Pat. No. 5,837,837, which disclosed the caspase 8 involvement in hematopoietic cells (Col 4-5). Zhang et al. doesn't have to give guidance as to how to determine if hematopoiesis is inhibited, since their disclosure meets all the method steps of the claims. Therefore, the Zhang et al reference is as much enabled, if not even more, than the instant Application. Moreover, Applicant is arguing limitations that are not present in the claims.

Conclusion

7. Claim 63 would be allowable if written as an independent claim. Claims 2, 3, 69 and 71 are not allowed.

8. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire **THREE MONTHS** from the mailing date of this action. In the event a first reply is filed within **TWO MONTHS** of the mailing date of this final action and the advisory action is not

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mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to ELLY-GERALD STOICA whose telephone number is (571)272-9941. The examiner can normally be reached on 8:30-17:00 M-F.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Manjunath N. Rao can be reached on (571) 272-0939. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Lorraine Spector/
Primary Examiner, Art Unit 1647